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Published in:
Clinical Microbiology and Infection

DOI:
[10.1016/j.cmi.2017.08.019](https://doi.org/10.1016/j.cmi.2017.08.019)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Plantinga, N. L., de Smet, A. M. G. A., Oostdijk, E. A. N., de Jonge, E., Camus, C., Krueger, W. A., ... Bonten, M. J. M. (2018). Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta-analysis. *Clinical Microbiology and Infection*, 24(5), 505-513. <https://doi.org/10.1016/j.cmi.2017.08.019>

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Original article

Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta-analysis[☆]N.L. Plantinga^{1,2,*}, A.M.G.A. de Smet⁴, E.A.N. Oostdijk^{2,3}, E. de Jonge⁵, C. Camus⁷, W.A. Krueger⁸, D. Bergmans⁶, J.B. Reitsma¹, M.J.M. Bonten^{1,2}¹ Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands² Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands³ Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands⁴ Department of Critical Care, University of Groningen, Groningen, The Netherlands⁵ Department of Intensive Care, Leiden University Medical Center, Leiden, The Netherlands⁶ Department of Intensive Care, Maastricht University Medical Centre, Maastricht, The Netherlands⁷ Department of Infectious Diseases and Intensive Care Medicine, Pontchaillou Hospital, University Hospital Centre Rennes, Rennes, France⁸ Department of Anesthesiology and Intensive Care, Clinics of Constance, Constance, Germany

ARTICLE INFO

Article history:

Received 14 August 2017

Received in revised form

23 August 2017

Accepted 23 August 2017

Available online 1 September 2017

Editor: L. Leibovici

Keywords:

Effect modification

Individual patient data meta-analysis

Intensive care unit

SDD

Selective digestive decontamination

Selective oropharyngeal decontamination

SOD

ABSTRACT

Objectives: Selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD) improved intensive care unit (ICU), hospital and 28-day survival in ICUs with low levels of antibiotic resistance. Yet it is unclear whether the effect differs between medical and surgical ICU patients. **Methods:** In an individual patient data meta-analysis, we systematically searched PubMed and included all randomized controlled studies published since 2000. We performed a two-stage meta-analysis with separate logistic regression models per study and per outcome (hospital survival and ICU survival) and subsequent pooling of main and interaction effects.

Results: Six studies, all performed in countries with low levels of antibiotic resistance, yielded 16 528 hospital admissions and 17 884 ICU admissions for complete case analysis. Compared to standard care or placebo, the pooled adjusted odds ratios for hospital mortality was 0.82 (95% confidence interval (CI) 0.72–0.93) for SDD and 0.84 (95% CI 0.73–0.97) for SOD. Compared to SOD, the adjusted odds ratio for hospital mortality was 0.90 (95% CI 0.82–0.97) for SDD. The effects on hospital mortality were not modified by type of ICU admission (p values for interaction terms were 0.66 for SDD and control, 0.87 for SOD and control and 0.47 for SDD and SOD). Similar results were found for ICU mortality.

Conclusions: In ICUs with low levels of antibiotic resistance, the effectiveness of SDD and SOD was not modified by type of ICU admission. SDD and SOD improved hospital and ICU survival compared to standard care in both patient populations, with SDD being more effective than SOD. **N.L. Plantinga, Clin Microbiol Infect 2018;24:505**

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Introduction

Selective decontamination is a widely used infection prevention strategy in Dutch intensive care units (ICUs). The concept entails

the preventive use of a mixture of topical antimicrobial agents with activity against aerobic Gram-negative bacteria, *Staphylococcus aureus* and yeasts to eradicate and prevent carriage with these pathogens, thereby preventing ICU-acquired infections. Selective oropharyngeal decontamination (SOD) consists of an oropharyngeal paste, usually containing tobramycin, colistin and amphotericin B, administered 4 times a day. Selective digestive decontamination (SDD) contains the same paste, supplemented with a suspension (with the same antimicrobial agents) administered through the nasogastric tube and a 4-day course of intravenously administered cephalosporins (usually cefotaxime). The

[☆] Presented in part at the 2016 annual meeting of the European Congress of Clinical Microbiology and Infectious Diseases (abstract O387).

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effects on patient outcome have been extensively investigated in ICUs with low levels of antibiotic resistance and include a reduction in ICU mortality, hospital mortality, 28-day mortality and ICU-acquired bacteraemia [1–3]. The two largest, and most recent, studies compared the effectiveness of SDD and SOD, with a significant survival benefit for SDD in one study [4] and a comparable effect in the other [1].

ICUs admit patients with large differences in age, reason for admission and disease severity, and thereby host a markedly heterogeneous population. It has been advocated that the (beneficial) effects of treatment should be investigated in more depth to identify those groups of patients who may benefit and those who may not benefit at all [5]. For SDD and SOD, it is unknown whether its effectiveness differs between surgical and medical patients, as the pathology and disease severity at ICU admission may vary between these two groups. Medical patients have on average longer hospitalization before ICU admission, and surgical patients more frequently have delayed intestinal passage. These characteristics may differently affect the capacity of SDD and SOD to eradicate existing and prevent new bacterial carriage and thus the effectiveness of these interventions in both patient groups.

In a traditional meta-analysis of 21 trials published between 1987 and 1996, SDD was associated with lower mortality and nosocomial infection rates in ICUs in which at least 75% of the patients included in the studies had been admitted after trauma or major surgery (11 studies), but not in ICUs in which less than 75% of admitted patients were categorized as having experienced trauma or major surgery (ten studies) [6]. In a subgroup analysis by the Dutch SOD-SDD Trialists' Group, SOD was associated with improved 28-day survival in the subgroup of nonsurgical patients only, whereas SDD was not associated with a difference in effectiveness between surgical and nonsurgical patients [7]. New and large studies have been performed since 1996, and the subgroup analysis mentioned originated from a single study that has not yet been replicated. In an individual patient data meta-analysis, there is more flexibility and power to examine whether treatment effects differ between subgroups. Furthermore, it avoids ecologic bias, which can be present when examining subgroups using meta-regression based on aggregate data [8,9].

We therefore performed an individual patient data meta-analysis to determine whether the effects of SDD and SOD differ between surgical and medical patients.

Methods

Data collection

We performed an individual patient data meta-analysis and included randomized controlled trials (RCTs) and cluster randomized trials (CRTs) with crossover that were performed in mixed adult ICUs and that were published between 2000 and 2016 (Supplementary Fig. 1). We excluded studies that only admitted either trauma, surgical or medical patients because these did not allow assessment of effect modification (also known as interaction) by admission type, as well as studies in paediatric or very specific ICU populations. Studies were identified through a systematic PubMed search including synonyms for domain, determinant and design without language restrictions or filters (9 March 2017). References of three previous meta-analyses were checked for missed trials [10–12]. First authors were asked to share a minimal set of individual patient data, including age, sex, disease severity, admission type and information on at least one of the two outcomes.

Our primary outcome was hospital survival, and the secondary outcome was ICU survival. From each study, we included all ICU

admissions of patients who had received the intervention or control measure at least once (intention to treat) and performed a complete case analysis. For both outcomes, comparisons were made among SDD, SOD and patients who had received either placebo or standard care (control group). The analysis for hospital survival was limited to the first inclusion within each hospital admission. The classification of patients into surgical and medical admissions was performed according to the original study definitions (Table 1). Trauma patients for whom it was unknown whether they had undergone surgery were reclassified as surgical admissions. To be included, ethical permission had to have been obtained within each individual study.

Statistical analysis

We performed a two-stage meta-analysis in which we first performed a separate logistic regression analysis within each study and for each outcome. Within each of these analyses, two models were fitted, one with an interaction between treatment and admission type to assess whether the effect of SDD and SOD differed between medical and surgical admissions, and one without this interaction term to estimate the main effect of SDD and SOD. These logistic models per study were stratified for study centre (as separate intercepts), thereby correcting for clustering. Because of the possibility of differences in baseline characteristics in cluster randomized trials, we also adjusted for age, sex, admission type (medical or surgical) and Acute Physiology and Chronic Health Evaluation (APACHE) II/IV score, as well as, when available, mechanical ventilation at ICU admission by adding these as main effects to the model. The estimated treatment effects from each study were meta-analysed in the second stage. We used random-effects or fixed-effect (depending on the degree of heterogeneity) meta-analytical techniques to obtain a pooled treatment effect across studies using inverse variance weighting. Heterogeneity in main treatment and interaction effects were assessed visually using forest plots and the I^2 statistic.

SPSS Statistics 21 (IBM SPSS, Chicago, IL, USA) was used for preparation of the data set, and RStudio 0.99.903 (<https://www.rstudio.com/>) was used for statistical analysis (packages lme4 [13], mvmeta [14] and metaphor [15]) (R; R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>).

Results

Included studies

The PubMed search yielded 265 articles published between 2000 and 2016, of which six original studies were eligible for inclusion (Supplementary Fig. 1). All authors provided individual patient data (Table 1). In four RCTs, either SDD or SOD was compared to a control intervention [2,3,16,17], in one CRT a comparison between all three arms was performed and in the largest CRT SOD and SDD were compared head to head [14]. Three studies were blinded [3,16,17] and the other studies [1,2,4] had a cluster design, which excludes the possibility of blinding but prevents the occurrence of contamination (i.e. treated patients protecting control patients from acquired colonization and infection). In total 29 different hospitals from three different countries participated in these studies, eight of which took part in two studies. Sample sizes ranged from 226 to 9206 hospital admissions and 9773 ICU admissions per study. Information on hospital survival was not available from two RCTs; for one study, 60-day survival status was used as proxy (for ICU survivors) [3]; the other study was excluded from the analysis of hospital survival [17].

Table 1
Study characteristics

Study	Bergmans 2001 [16]	Krueger 2002 [3]	De Jonge 2003 [2]	Camus 2005 [17]	De Smet 2009 [1]	Oostdijk 2017 [4] ^a
DOI	10.1164/ajrccm.164.3.2005003	10.1164/rccm.2105141	10.1016/S0140-6736(03)14409-1	10.1097/01.CCM.0000152224.01949.01	10.1056/NEJMoa0800394	10.1001/jama.2017.1282
Country	The Netherlands	Germany	The Netherlands	France	The Netherlands	The Netherlands
Design	RCT, double blind	RCT, double blind (randomization stratified by APACHE II)	RCT, nonblinded (individual randomization to unit)	RCT, double blind (4 × 4 factorial design)	CRT with crossover	CRT with crossover
Control group	Placebo	Placebo	Standard care	Placebo/placebo; placebo/mupirocin nasal ointment	Standard care	NA
SOD antibiotics	GEN, CST, VAN	NA	NA	NA	TOB, CST, Amph B	TOB, CST, Amph B
SDD antibiotics	NA	GEN, CST; CIP iv	TOB, CST, Amph B; CTX iv	CST, TOB/placebo; CST, TOB/mupirocin nasal ointment (no iv component)	TOB, CST, Amph B; CTX iv	TOB, CST, Amph B; CTX or CRO iv
No. of hospitals	2	2	1	3	13	16
Inclusion period	Sep 1994–Dec 1996	Apr 1990–Aug 1992	Sep 1999–Dec 2001	Apr 1996–Oct 1998	May 2004–Jul 2006	Aug 2009–Feb 2013
Inclusion criteria (original)	Intubation within 24 hours, expected MV >2 days and age ≥16 years; evaluable if >2 days in study	Expected ICU LOS >48 hours, age ≥18 years, at least one additional condition ^b	Expected MV >48 hours or expected ICU LOS >72 hours (adults)	Expected MV >48 hours, intubated <48 hours at inclusion, age ≥18 years	Expected MV >48 hours or expected ICU LOS >72 hours	Expected ICU LOS >48 hours; evaluable if patient received at least one dose and/or had an ICU LOS of >48 hours
Definition of 'surgical admission'	Reason for ICU admission was postoperative/surgical (according to treating ICU physician); 'trauma' was recoded into surgical admission	'postoperative patient'	According to NICE criteria; surgery in week before ICU admission	Those admitted to ICU immediately after surgery from operating room; 'trauma' was recoded into surgical admission	Reason for ICU admission was postoperative/surgical according to treating ICU physician	Received any type of surgery in week before ICU admission
No. of ICU admissions (complete cases)	226 (226)	527 (527)	934 (926)	515 (515)	5923 (5914)	9773 (9768)
No. of hospital admissions (complete cases)	226 (226)	527 (527)	933 (925)	515 (0)	5650 (5643)	9206 (9201)

Amph B, amphotericin B; APACHE, Acute Physiology and Chronic Health Evaluation (measure of disease severity); CIP, ciprofloxacin; CRO, ceftriaxone; CRT, cluster randomized trial; CST, colistin; CTX, cefotaxime; GEN, gentamicin; ICU, intensive care unit; MV, mechanical ventilation; NA, not applicable; NICE, Nationale Intensive Care Evaluatie (www.stichting-nice.nl); RCT, randomized controlled trial; SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination; TOB, tobramycin; VAN, vancomycin.

^a This is only study with APACHE IV instead of APACHE II, without a control group and without information on ventilation at baseline (MV).

^b Additionally, at least one of following conditions had to be present: expected intubation period of more than 24 hours, respiratory failure (PaO₂ of <55 mm Hg on room air), thoracic or abdominal surgery within preceding 24 hours, severe organ dysfunction at admission, increased risk of aspiration caused by swallowing disorder, chronic obstructive pulmonary disease, immunosuppressive therapy or advanced age (>70 years).

Table 2Patient characteristics per first inclusion within unique hospital admission, including incomplete cases ($n = 14$ for main models; $n = 22$ for model effect modification)

Characteristic	SDD, n (%) ($n = 7718$)	SOD, n (%) ($n = 6326$)	Control, n (%) ($n = 3013$)
Men, n (%)	4699 (60.9)	3918 (61.9)	1853 (61.6)
Age, years, mean (SD) ^a	62.3 (16.0)	62.3 (15.9)	60.3 (16.8)
APACHE II score, mean (SD) ^a	19.5 (7.7)	19.6 (8.2)	19.0 (7.8)
APACHE IV score, mean (SD) ^b	81.7 (33.8)	82.1 (33.4)	NA
SAPS II score, mean (SD) ^c	46.5 (15.3)	NA	45.0 (14.4)
Mechanical ventilation at baseline, n (%) ^d	2698 (91.6)	1788 (94.5)	2699 (89.6)
Medical admissions, n (%)	4522 (58.6)	3841 (60.7)	1494 (49.7)
Surgical admissions, n (%)	3193 (41.4)	2485 (39.3)	1514 (50.3)
Study describing patient origin, n (%)			
Bergmans [16]		87 (1.4)	139 (4.6)
Krueger [3]	265 (3.4)		262 (8.7)
De Jonge [2]	466 (6.0)		467 (15.5)
Camus [17] ^e	259 (3.4)		256 (8.5)
De Smet [1]	1955 (25.3)	1806 (28.5)	1889 (62.7)
Oostdijk [4]	4773 (61.8)	4433 (70.1)	

APACHE, Acute Physiology and Chronic Health Evaluation (measure of disease severity); NA, not applicable; SAPS, Simplified Acute Physiology Score (measure of disease severity); SD, standard deviation; SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination.

^a Not available from studies of Oostdijk et al. [4] and Camus et al. [17].^b Only available from Oostdijk et al. [4].^c Only available from Camus et al. [17].^d Not available from Oostdijk et al. [4].^e This study was not included in analysis on hospital survival.

In all, 20 126 records were obtained from the original studies, comprising 16 528 hospital admissions and 17 884 ICU admissions from 16 540 unique patients available for complete case analysis (Supplementary Fig. 2). There were slight imbalances in baseline characteristics, which were partly due to imbalances between study groups in some of the studies and partly due to differences between studies, as five studies did not have all three treatment arms (Table 2). There were 9857 hospital admissions (57.8%) with a medical and 7192 (42.2%) with a surgical reason for ICU admission.

Hospital mortality

Crude hospital mortality was 29.5% (2199/7458) for SDD, 31.5% (1994/6326) for SOD and 32.4% (894/2756) among control groups (Table 3). The main treatment effects and the interaction terms of individual studies were fairly similar within each comparison,

with largely overlapping confidence intervals (Figs. 1 and 2, I^2 statistic 1%). One exception included the comparison of SDD vs. SOD (main effect), where an adjusted odds ratio (aOR) of 1.01 was found in the first and an aOR of 0.85 in the second study (Fig. 3, I^2 statistic 72.4%). Because the number of studies was limited, all estimates were pooled using inverse variance weighting with fixed effects. Resulting aORs (95% confidence intervals (CIs)) for hospital mortality were 0.82 (0.72–0.93) for SDD vs. control, 0.84 (0.73–0.97) for SOD vs. control and 0.90 (0.82–0.97) for SDD vs. SOD (Table 3, Figs. 1–3). Interactions between treatment and admission type were not statistically significant within each of the three comparisons, as illustrated by adjusted relative odds ratios (aORs) (95% CIs) for surgical vs. medical patients for SDD vs. control of 0.95 (0.74–1.21, p 0.66), for SOD vs. control of 1.03 (0.77–1.37, p 0.87) and for SDD vs. SOD of 0.94 (0.79–1.11, p 0.47) (Table 3, Figs. 1–3).

Table 3

Hospital and ICU mortality in all patients and in surgical and medical patients (two-stage meta-analysis, fixed pooled effect)

Mortality	Crude mortality			aOR (95% CI) for: ^b		
	SDD	SOD	Control	SDD vs. control	SOD vs. control	SDD vs. SOD
Hospital mortality^a						
Main (n 16 540)	2199/7458, 29.5%	1994/6326, 31.5%	894/2756, 32.4%	0.82 (0.72–0.93); NNT 23.7	0.84 (0.73–0.97); NNT 26.9	0.90 (0.82–0.97); NNT 43.2
Medical (n 9417)	1423/4298, 33.1%	1322/3841, 34.4%	472/1278, 36.9%	0.84 (0.71–1.00); NNT 25.4	0.83 (0.68–1.01)	0.91 (0.82–1.01)
Surgical (n 7115)	774/3157, 24.5%	672/2485, 27.0%	422/1473, 28.6%	0.79 (0.66–0.94); NNT 22.0	0.85 (0.68–1.05)	0.87 (0.76–1.00); NNT 37.3
Measure of interaction on multiplicative scale: ratio of aORs (95% CI), surgical vs. medical				0.95 (0.74–1.21); p 0.66	1.03 (0.77–1.37); p 0.87	0.94 (0.79–1.11); p 0.47
ICU mortality						
Main (n 17 898)	1683/8086, 20.8%	1537/6701, 22.9%	753/3111, 24.2%	0.74 (0.65–0.84); NNT 19.4	0.85 (0.73–1.00); NNT 35.7	0.86 (0.78–0.94); NNT 38.2
Medical (n 10 507)	1161/4810, 24.1%	1048/4137, 25.3%	419/1560, 26.9%	0.81 (0.68–0.95); NNT 24.8	0.93 (0.75–1.14)	0.89 (0.80–0.99); NNT 45.9
Surgical (n 7383)	520/3273, 15.9%	489/2564, 19.1%	334/1546, 21.6%	0.64 (0.53–0.79); NNT 15.3	0.77 (0.61–0.97); NNT 24.1	0.80 (0.69–0.93); NNT 31.0
Measure of interaction on multiplicative scale: ratio of aORs (95% CI) surgical vs. medical				0.82 (0.62–1.08); p 0.15	0.83 (0.61–1.14); p 0.25	0.89 (0.74–1.08); p 0.25

aOR, adjusted OR; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; NNT, number needed to treat (calculated using pooled aORs and overall proportion of patients who died in comparator group (control for first two comparisons and SOD for latter; in settings with different mortality risks, NNT may be different)); SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination.

^a For SDD vs. control analysis on hospital mortality includes three and on ICU mortality four studies; for SOD vs. control and SDD vs. SOD, analyses on both outcomes include same studies.^b Models of multicentre studies were corrected for centre; models of cluster randomized trials were corrected for age, sex, admission type (medical or surgical), APACHE II/IV score and, when available, mechanical ventilation at ICU admission.

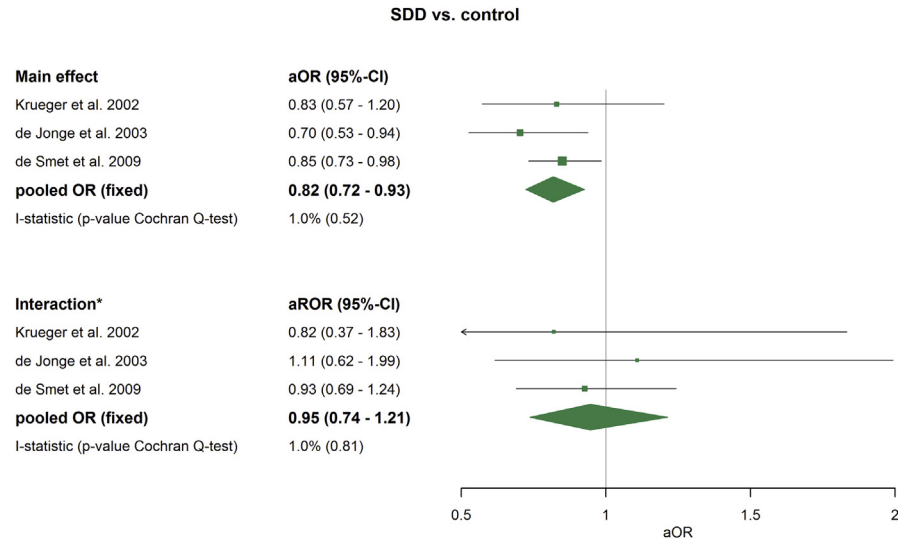


Fig. 1. Forest plots of effects of SDD on hospital mortality: pooled treatment effects and interaction terms (treatment with admission type).

*Surgical vs. medical; aOR, adjusted odds ratio; aROR, adjusted relative odds ratio; SOD, selective oropharyngeal decontamination; SDD, selective digestive decontamination.

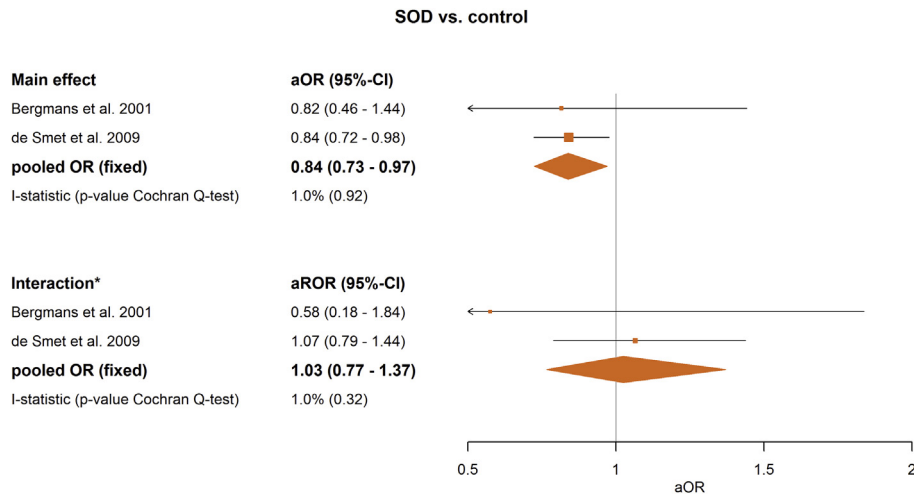


Fig. 2. Forest plots of effects of SOD on hospital mortality: pooled treatment effects and interaction terms (treatment with admission type).

*Surgical vs. medical; aOR, adjusted odds ratio; aROR, adjusted relative odds ratio; SOD, selective oropharyngeal decontamination; SDD, selective digestive decontamination.

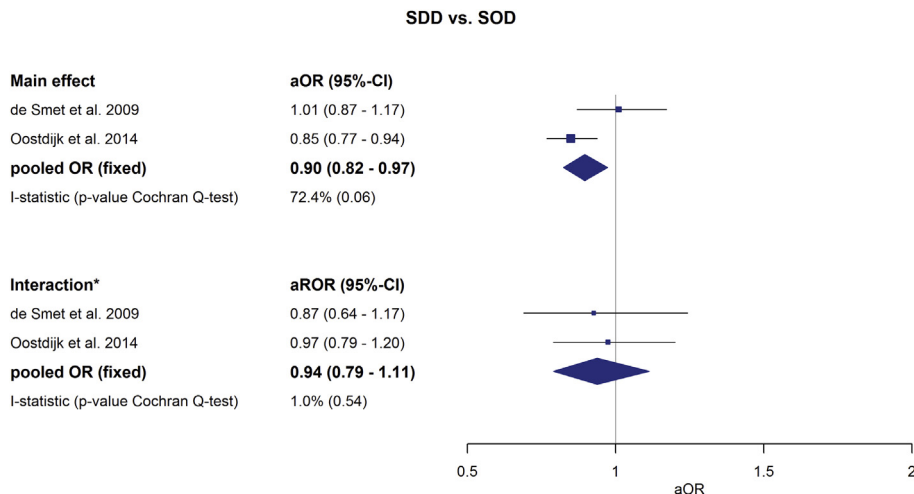


Fig. 3. Forest plots of effects of SDD compared to SOD on hospital mortality: pooled treatment effects and interaction terms (treatment with admission type).

*Surgical vs. medical; aOR, adjusted odds ratio; aROR, adjusted relative odds ratio; SOD, selective oropharyngeal decontamination; SDD, selective digestive decontamination.

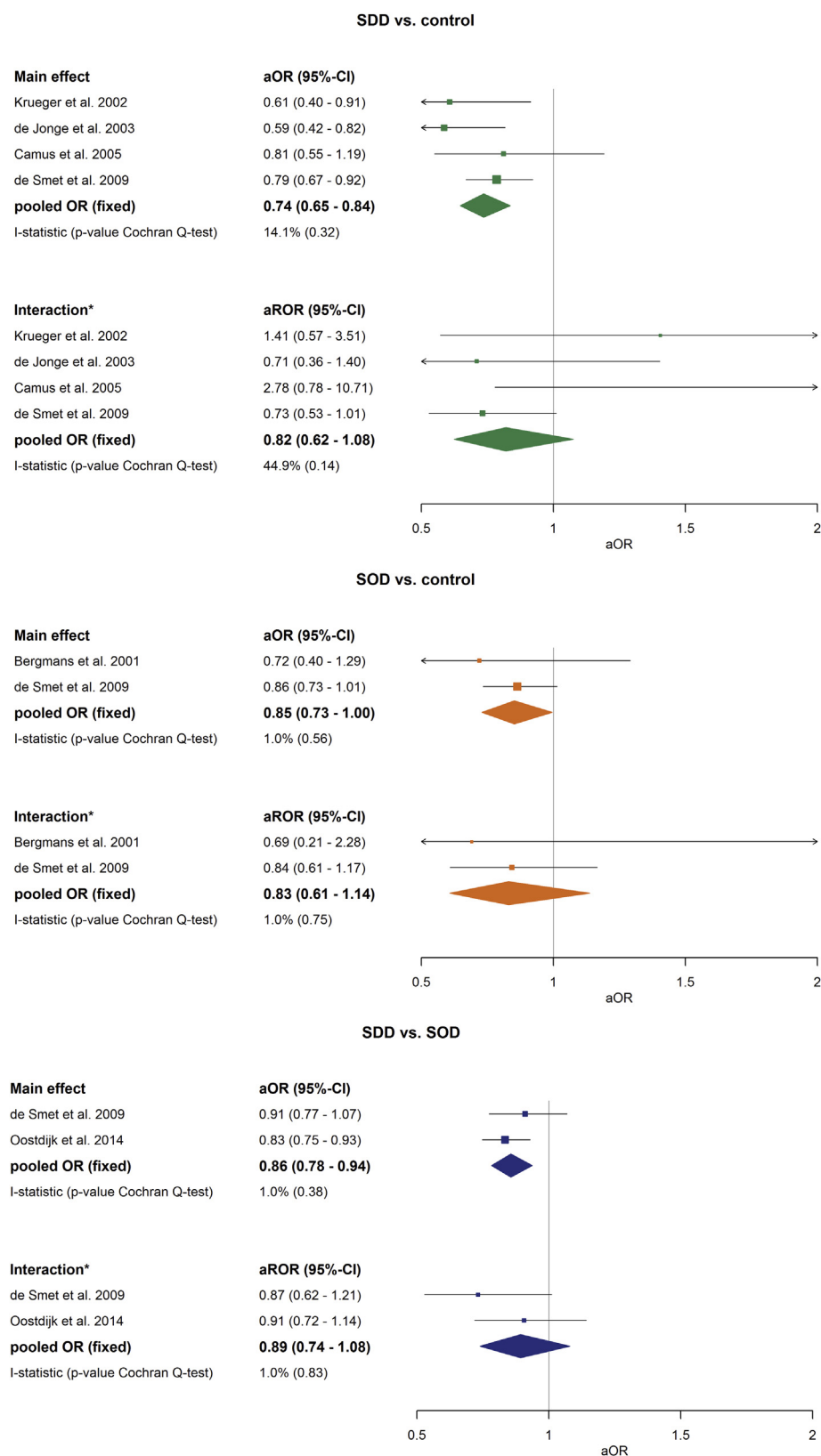


Fig. 4. Forest plots of effects of SDD and SOD on ICU mortality: pooled treatment effects and interaction terms (treatment with admission type).

*Surgical vs. medical; aOR, adjusted odds ratio; aROR, adjusted relative odds ratio; SOD, selective oropharyngeal decontamination; SDD, selective digestive decontamination.

ICU mortality

Crude ICU mortality was 20.8% (2199/7458) for SDD, 22.9% (1994/6326) for SOD and 24.2% (894/2756) in the control groups (Table 3). The forest plots demonstrate low heterogeneity in main treatment effects; in each contributing study, SDD and SOD were effective or showed a trend towards effectiveness compared to control, with SDD being more effective than SOD. Estimates were pooled using fixed effects, resulting in aORs (95% CIs) for ICU mortality of 0.74 (0.65–0.84) for SDD vs. control, 0.85 (0.73–1.00) for SOD vs. control and 0.86 (0.78–0.94) for SDD vs. SOD (Table 3, Fig. 4). With regard to the interaction effects, some heterogeneity was present, with trends towards better effectiveness of SDD for surgical patients compared to control in two studies and for medical patients in the other two studies (I^2 statistic 45%). For SOD vs. control and SDD vs. SOD, the estimated interactions pointed in the same direction in all studies. After fixed effects pooling, there was for both SDD and SOD, compared to control patients, a trend towards higher effectiveness in surgical than in medical patients (aROR (95% CI) 0.82 (0.62–1.08) and 0.83 (0.61–1.14)), but differences in effectiveness between the surgical and medical subgroups were not statistically significant (p of interaction term 0.15 and 0.25 respectively). Also for SDD vs. SOD, there was no interaction between treatment effect and admission type (aROR 0.89 (95% CI 0.74–1.08), p 0.25).

The aOR within medical and surgical patients indicate that among surgical patients, the effect of SDD (and to a lesser extent SOD) on ICU survival appeared to be stronger than the effects on hospital survival (Table 3). Because these ratios are not based on data coming from the same studies (four vs. three studies), we performed an unplanned additional analysis among so-called ICU survivors from the three studies that provided data for both outcomes, which yielded a trend towards increased hospital mortality among surgical patients who had been treated with SDD and had survived their first ICU admission (aOR 1.26 (95% CI 0.95–1.67), Supplementary Table 1) compared to control. However, this aOR was nonsignificant (p 0.11), as was the corresponding interaction term, indicating this may also be a chance finding. The opposite trend was observed for medical patients receiving SOD, where the aOR (95% CI) tended to be lower for hospital mortality (0.83 (0.68–1.01)) than for ICU mortality (0.93 (0.75–1.14)) (Table 3).

Discussion

In this individual patient data meta-analysis, the effects of both SDD and SOD on hospital survival and ICU survival were not modified by the type of ICU admission (surgical or medical). We precisely quantified the effectiveness of these treatments in a large population and confirmed the recent findings that SDD is more effective at improving hospital and ICU survival than SOD.

There was no effect modification by admission type in any of the three comparisons. Moreover, our findings provide further evidence that SDD is more efficacious than SOD in improving patient survival [4]. SDD differs from SOD in the fact that in addition to the oropharyngeal paste, patients are treated with a gastrointestinal suspension (containing the same antibiotics) and receive a 4-day course of third-generation cephalosporins, which consisted of cefotaxime in 24 and ceftriaxone in five study centres. Both differences may contribute to the difference in effectiveness.

Decontamination of the gastrointestinal tract may reduce the risk of gut-derived sepsis—and thereby mortality—through a reduction in systemic translocation of pathogens from the gut [18]. In prior studies, SDD was more effective at preventing ICU-acquired

bacteraemia with *Enterobacteriaceae* than SOD, and rectal colonization with Gram-negative bacteria was associated with increased risk of ICU-acquired bacteraemia with these pathogens [14,19]. Also, effective gastrointestinal decontamination may reduce respiratory colonization and infection with these pathogens, through reductions in translocation via the gut–lymph axis, (micro-)aspiration and exogenous translocation [18]. In fact, SDD was associated with a statistically significant reduction in the risk of respiratory colonization with *Enterobacteriaceae* (and not with primarily respiratory pathogens such as *Pseudomonas aeruginosa*) compared to SOD [20].

The 4-day course of cephalosporins—included in the SDD regimen with the aim to treat any incubating respiratory tract infection before decolonization is achieved—may also improve outcome. Many patients enrolled onto the SOD and control groups also received antibiotics during the first days of ICU admission for therapeutic reasons. An analysis of the original study data of de Smet et al. [1] found that the proportion of SDD-treated patients receiving intravenous antibiotics compared to SOD was 13% to 25% higher between days 1 and 5, but lower from day 7 onwards (absolute difference; Supplementary Table 2 and Supplementary Fig. 3). The relative contribution of the gastrointestinal suspension vs. the 4-day course of intravenous cephalosporins to the difference in effectiveness of SDD and SOD cannot be disentangled from these data.

We observed that in surgical patients, SDD appeared more effective at improving ICU survival than hospital survival, suggesting that part of the benefit from SDD with regard to ICU survival was lost before hospital discharge. An opposite trend was observed among medical patients receiving SOD, with a more profound effect of SOD on in-hospital mortality than on ICU mortality. Up front, we chose hospital survival as our primary outcome because of its clinical relevance. These findings provide further support for using hospital mortality as the primary outcome in future studies.

Using individual patient data from 17 898 ICU admissions in 29 hospitals in three countries has several additional distinct benefits over performing a meta-analysis with aggregate data. Firstly, and most importantly, it allowed us to assess interaction without the risk of aggregation bias and with more statistical power [9]. Secondly, we created a database with transparent inclusion criteria and adopted a uniform statistical analysis per study, correcting for confounding where necessary. The quality of the data was high, as many variables were provided with few missing data (<0.2%, Table 1).

We performed a two-stage meta-analysis—as opposed to a one-stage meta-analysis (OSM) in which all studies are analysed together in one model—because it allowed assessment of within-trial-level interactions, thereby preventing aggregation bias [9,21]. Although within-trial-level interactions may be estimated separately from across-trial level interactions in an OSM (by centring the covariate of interest per study), we considered that this approach could not fully prevent bias in our data because the three treatment arms are not represented in all studies. In addition, a two-stage approach enabled correction for confounding by all relevant variables that were available within each CRT, which would have required multiple imputation in an OSM. Finally, the results of a two-stage meta-analysis are more easily interpretable than the results of an OSM, with visualization of the results per study in forest plots and the possibility to calculate clinically meaningful odds ratios (ORs) from the interaction terms.

This study also has limitations. Firstly, study selection was limited to publications from 2000 onwards to enhance generalizability of findings to today's practice, yet in the three smallest studies, all patients were recruited between 1990 and 2000. When

we extended the search to studies that recruited patients from 1990 onwards, we identified two additional eligible studies from which individual patient data were not available [22,23]. Three RCTs altogether including 506 patients were excluded because they recruited trauma patients only, which precludes assessment of effect modification by admission type. In one of these, the effect of SDD on survival was assessed with an OR of 0.75 (95% CI 0.40–1.37) for late mortality compared to placebo [24]. Secondly, all studies were performed in settings with low levels of antibiotic resistance (Supplementary Table 3). This limits the generalizability of our findings to settings with <10% rectal colonization with highly resistant microorganisms and <3% of methicillin-resistant *S. aureus* and vancomycin-resistant enterococci. However, we also consider the absence of heterogeneity due to different bacterial ecology a study strength. A cluster randomized trial in ICUs with higher levels of antibiotic resistance has recently been finalized (ClinicalTrials.gov identifier NCT02208154). Thirdly, any individual patient data meta-analysis relies on the availability of original data and definitions used. Although we obtained the original data from all studies identified, it was not possible to recode the original definitions of surgical and medical admissions to a single identical definition. The chosen definition, using the criteria from the original studies, may have introduced heterogeneity within the subgroups, thereby biasing the potential difference in effectiveness between the subgroups towards null. However, it also enhances generalizability to ICUs using different definitions for admission type, thereby responding to the pragmatic nature of the research question. Furthermore, we did not account for competing events. We chose to perform a logistic regression analysis because hospital survival is a clinically relevant outcome, and we prefer the interpretation of ORs from logistic regression over hazards ratios that result from survival analysis. We justify this choice because follow-up was complete and differences in hospital discharge policy per study arm are not to be expected. Finally, despite obtaining individual patient data from all studies that met our inclusion criteria, our study may have been underpowered to identify effect modification. This may have occurred for the comparison of SOD to controls, where >95% of SOD patients were derived from a single study [1], which also explains the wide CIs for the comparison of SOD-treated patients with controls.

Conclusions

On the basis of the individual data of 16 528 patients from six randomized studies in settings with low levels of antibiotic resistance, the effectiveness of SDD and SOD was not modified by type of ICU admission. SDD and SOD improved hospital and ICU survival compared to standard care in both surgical and medical patients, with SDD being more effective than SOD.

Acknowledgements

We acknowledge B. H. J. Wittekamp and C. H. van Werkhoven (Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands) for verification of data preparation and statistical analysis.

Transparency Declaration

NP and MB received funding from the EU 7th Framework Programme (Grant agreement number: 282512). All authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.cmi.2017.08.019>.

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